

Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 3

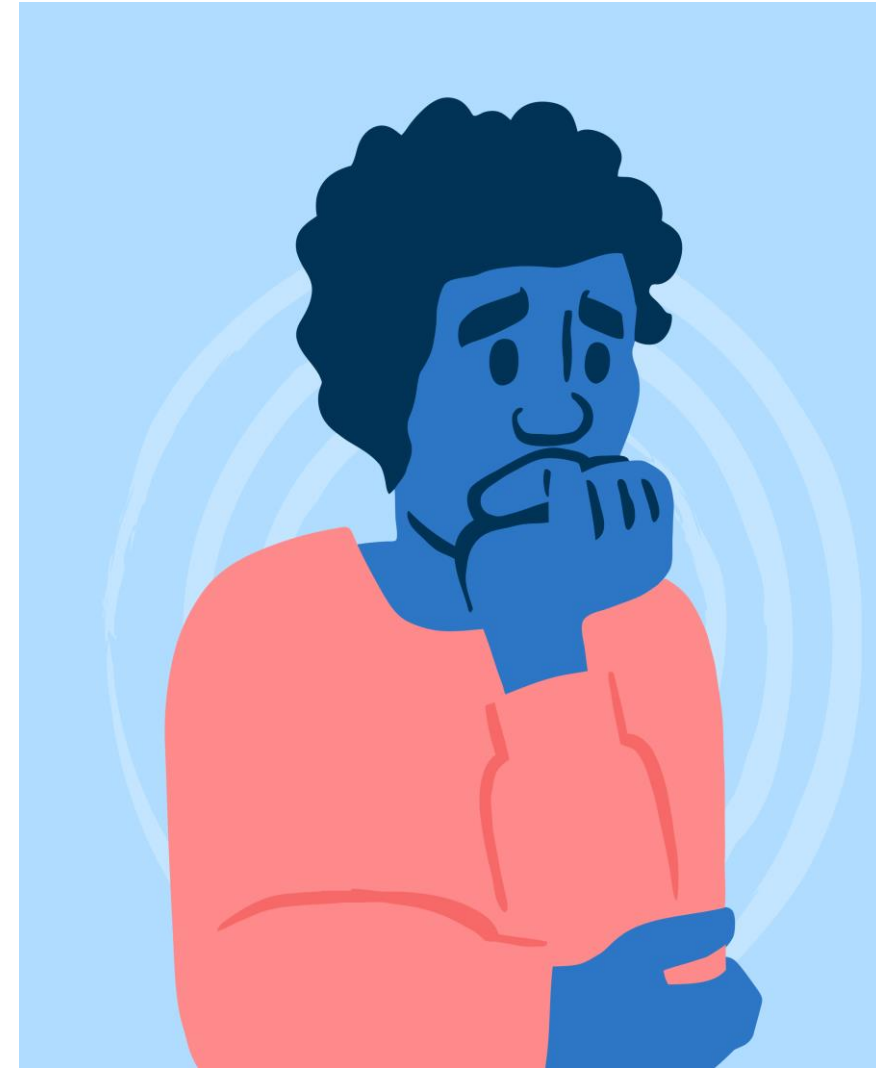


Anxiolytics & Hypnotics

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Anxiety

- **Anxiety** is an unpleasant state of tension, apprehension, or uneasiness (a fear that arises from either a known or an unknown source).
- The **physical symptoms** of severe anxiety are tachycardia, sweating, trembling, and palpitations and involve **sympathetic** activation.
- Episodes of **mild anxiety** are **common** life experiences and do **not** warrant treatment.
- However, **severe, chronic, debilitating anxiety** may be treated with **antianxiety** drugs (sometimes called anxiolytics) and/or some form of **psychotherapy**.



Anxiolytics

ANXIOLYTICS AND HYPNOTICS

BENZODIAZEPINES
<i>Alprazolam</i> XANAX
<i>Chlordiazepoxide</i> LIBRIUM
<i>Clonazepam</i> KLOPINOL
<i>Clorazepate</i> TRANXENE
<i>Diazepam</i> VALIUM, DIASAT
<i>Estazolam</i> GENERIC ONLY
<i>Flurazepam</i> GENERIC ONLY
<i>Lorazepam</i> ATIVAN
<i>Midazolam</i> GENERIC ONLY
<i>Oxazepam</i> GENERIC ONLY
<i>Quazepam</i> DORAL
<i>Temazepam</i> RESTORIL
<i>Triazolam</i> HALCION
BENZODIAZEPINE ANTAGONIST
<i>Flumazenil</i> GENERIC ONLY

OTHER ANXIOLYTIC DRUGS
Antidepressants VARIOUS (SEE CHAPTER 10)
<i>Bupirone</i> GENERIC ONLY
<i>Meprobamate</i> GENERIC ONLY
BARBITURATES
<i>Amobarbital</i> AMYTAL
<i>Pentobarbital</i> NEMBUTAL
<i>Phenobarbital</i> GENERIC ONLY
<i>Secobarbital</i> SECONAL

OTHER HYPNOTIC AGENTS
Antihistamines VARIOUS (SEE CHAPTER 37)
<i>Doxepin</i> SILENOR
<i>Eszopiclone</i> LUNESTA
<i>Ramelteon</i> ROZEREM
<i>Suvorexant</i> BELSOMRA
<i>Tasimelteon</i> HETLIJAZ
<i>Zaleplon</i> SONATA
<i>Zolpidem</i> AMBIEN, INTERMEZZO, ZOLPIMIST

BENZODIAZEPINES

- Benzodiazepines are **widely** used anxiolytic drugs.
- They have largely replaced **barbiturates and meprobamate** in treating anxiety and insomnia because benzodiazepines are generally considered **safer** and more **effective**.
- Certain antidepressants with **anxiolytic** action, such as **SSRIs**, are preferred in many cases
- **Nonbenzodiazepine** hypnotics and **antihistamines** may be preferable for **insomnia**.

BENZODIAZEPINES

- **Benzodiazepines** are classified according to the **duration of action** into:

Short half-life



3-8 Hours

*Alprazolam
Midazolam
Oxazepam
Triazolam*

Intermediate half-life



10-20 Hours

*Estazolam
Lorazepam
Temazepam*

Long half-life

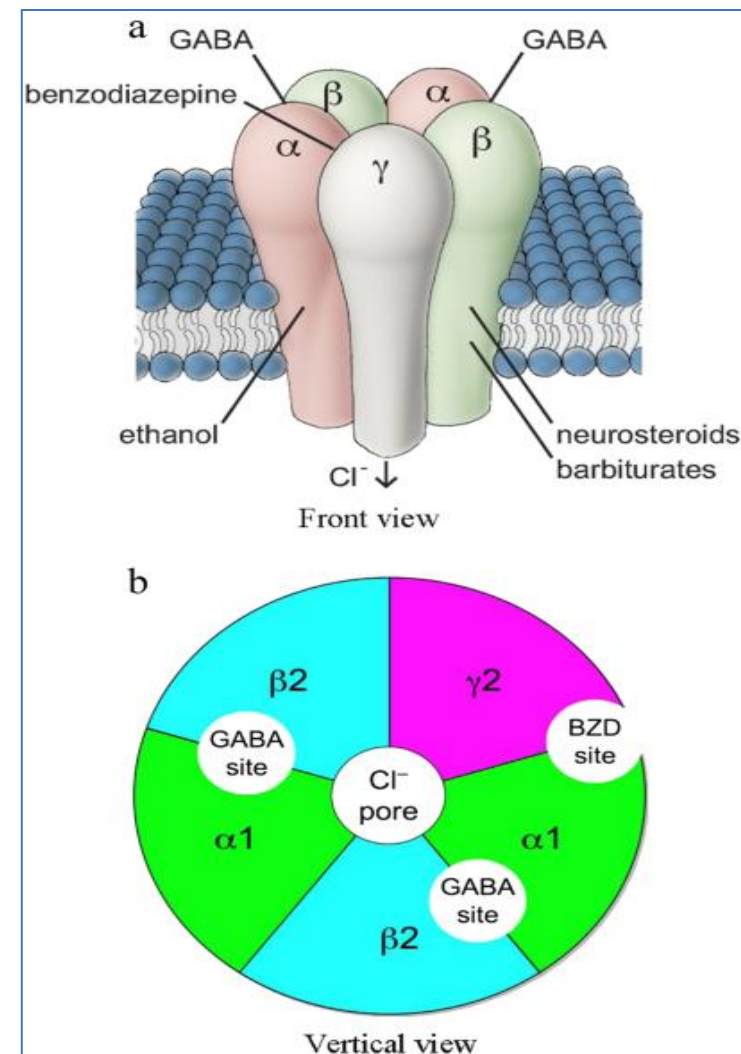


*Clorazepate
Chlordiazepoxide
Diazepam
Flurazepam
Quazepam*

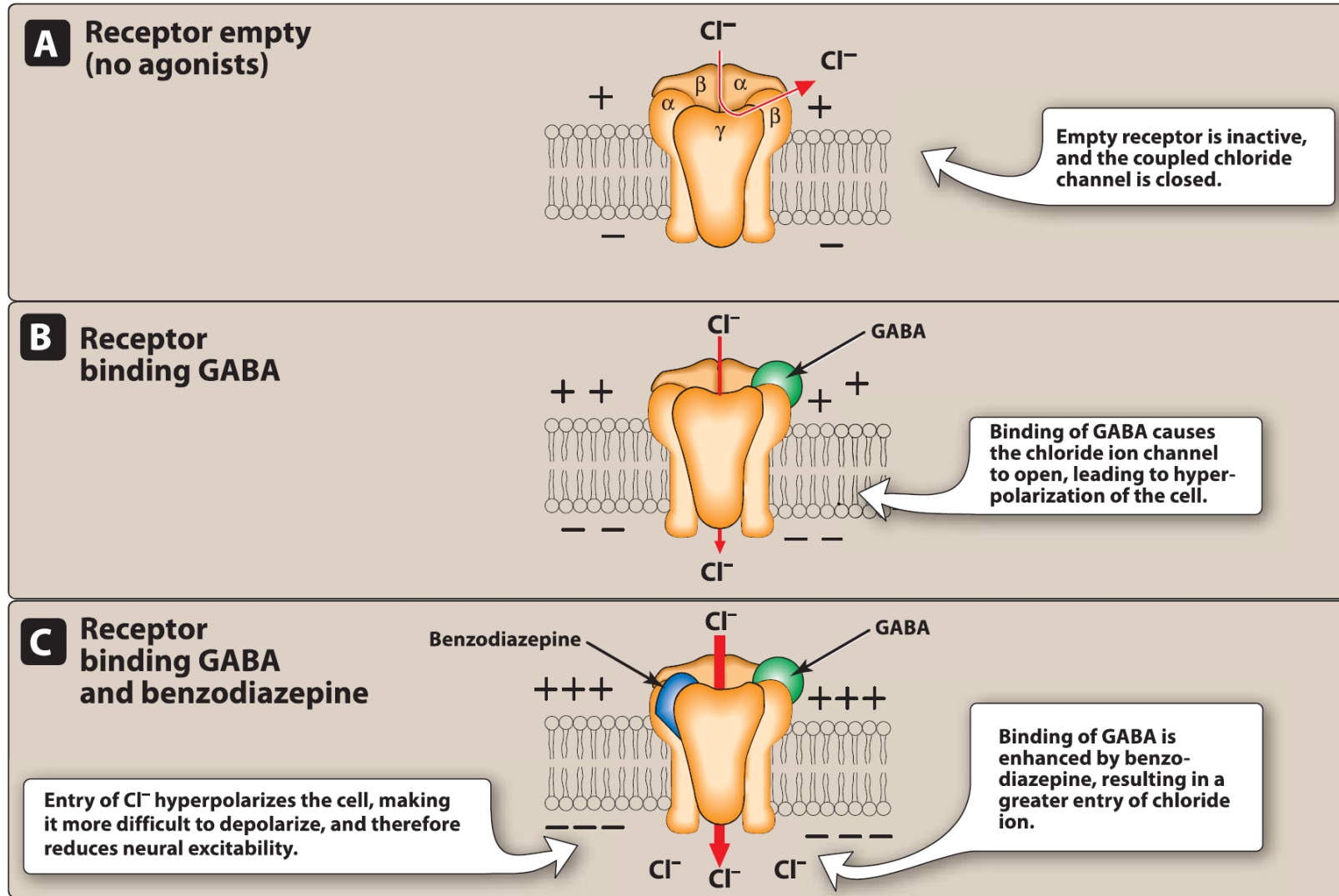
BENZODIAZEPINES

Mechanism of action:

- The target for benzodiazepine actions is the **γ -aminobutyric acid (GABA-A)** receptors, that composed of a combination of **five 2α , 2β , and γ subunits**.
- **BZDs** bind within the **interface** between the **α** and **γ** subunits
- **Binding** of GABA to its receptor triggers an **opening** of the central ion channel, allowing **chloride** through the pore.
- The **influx** of chloride ions causes **hyperpolarization** of the neuron and **decreases** neurotransmission by inhibiting the formation of action potentials.
- Common BZ receptor subtypes in the CNS are **BZ1** ($\alpha 1$ subunit) or **BZ2** ($\alpha 2$ subunit).
- Benzodiazepines **increase** the **frequency** of channel openings produced by GABA.



BENZODIAZEPINES



Schematic diagram of benzodiazepine–GABA–chloride ion channel complex

BENZODIAZEPINES

Actions:

1. Reduction of anxiety:

- At **low doses**, benzodiazepines are **anxiolytic**.
- The **anxiolytic** effects are mediated by the **$\alpha 2$ -GABA-A** receptors

2. Sedative/hypnotic:

- **All** benzodiazepines have **sedative** and **calming** properties, and **some** can produce **hypnosis** (artificially produced sleep) at **higher** doses.
- The **hypnotic** effects are mediated by the **$\alpha 1$ -GABA-A** receptors.

3. Anterograde amnesia:

- **Temporary** impairment of memory with the use of benzodiazepines is also mediated by the **$\alpha 1$ -GABA-A** receptors.
- The ability to learn and form **new memories** is also **impaired**.

BENZODIAZEPINES

Actions:

4. Anticonvulsant:

- **Several** benzodiazepines have **anticonvulsant** activity.
- This effect may be mediated by **α 1-GABAA** receptors.

5. Muscle relaxant:

- **At high doses**, the benzodiazepines **relax** the spasticity of skeletal muscle, probably by **increasing presynaptic inhibition** in the spinal cord, where the **α 2-GABA-A** receptors are largely located.
- **Baclofen** is a muscle relaxant that is believed to affect GABA receptors at the level of the spinal cord.

BENZODIAZEPINES

Therapeutic uses:

1. Anxiety disorders:

- Benzodiazepines are effective for the treatment of **anxiety symptoms secondary** to:
 - ✓ Panic disorder
 - ✓ Generalized anxiety disorder (GAD)
 - ✓ Social anxiety disorder
 - ✓ Performance anxiety
 - ✓ Posttraumatic stress disorder
 - ✓ Obsessive–compulsive disorder

BENZODIAZEPINES

Therapeutic uses:

1. Anxiety disorders:

- These drugs should be reserved for **severe anxiety only** and not used to manage the stress of everyday life.
- Because of their **addiction** potential, they should only be used for **short periods of time**.
- The **longer-acting agents**, such as clonazepam, lorazepam, and diazepam, are often **preferred** in those patients with anxiety that may require prolonged treatment.
- For **panic disorders**, alprazolam is effective for **short- and long-term** treatment, although it may cause **withdrawal** reactions in about **30%** of patients.

BENZODIAZEPINES

Therapeutic uses:

2. Sleep disorders:

- A **few** benzodiazepines are useful as hypnotic agents.
- These agents **decrease** the latency to sleep onset and **increase** stage II of non-rapid eye movement (REM) sleep.
- **Commonly** prescribed benzodiazepines for sleep disorders include intermediate-acting **temazepam** and short-acting **triazolam**.
- Long-acting **flurazepam** is rarely used, due to its extended half-life, which may result in excessive **daytime sedation**.



BENZODIAZEPINES

Therapeutic uses:

3. Amnesia:

- The **shorter-acting** agents are often employed as **premedication** for anxiety-provoking and unpleasant procedures, such as **endoscopy, dental procedures, and angioplasty**.
- They cause a form of **conscious sedation**, allowing the person to be **receptive to instructions** during these procedures.
- **Midazolam** is a benzodiazepine used to facilitate amnesia while causing sedation prior to anesthesia.

BENZODIAZEPINES

Therapeutic uses:

4. Seizures:

- **Clonazepam** is occasionally used as **adjunctive** therapy for certain types of seizures.
- **Lorazepam** and **diazepam** are the drugs of choice in terminating **status epilepticus**.

5. Muscular disorders:

- **Diazepam** is useful in the treatment of:
 1. **Skeletal muscle spasms**, such as occur in muscle strain
 2. **Spasticity** from degenerative disorders, such as multiple sclerosis and cerebral palsy

BENZODIAZEPINES

Pharmacokinetics:

1. Absorption and distribution:

- They are **lipophilic**, so they are **rapidly** and **completely** absorbed after **oral** administration, **distribute** throughout the body and penetrate the **CNS**.

2. Duration of action:

- Their half-lives are **important clinically**, because the duration of action may determine the therapeutic usefulness.
- Sometimes the clinical **duration of action** does **not correlate** with the actual **half-life**, this may be due to **receptor dissociation** rates in the CNS and subsequent **redistribution** to fatty tissues and other areas.

BENZODIAZEPINES

Pharmacokinetics:

3. Fate:

- Drug effects are terminated **not only** by excretion but also by redistribution.
- The benzodiazepines are excreted in the urine as **glucuronides** or **oxidized** metabolites.
- They are **not recommended** for use during **pregnancy**.
- **Nursing infants** may also be exposed to the drugs in breast milk.



BENZODIAZEPINES

Dependence

- **Psychological** and **physical** dependence on benzodiazepines can develop if **high doses** of the drugs are given for a **prolonged period**.
- **All** benzodiazepines are **controlled substances**.
- **Abrupt** discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures.
- Benzodiazepines with a **short elimination half-life**, such as **triazolam**, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated such as **flurazepam**.

BENZODIAZEPINES

Adverse effects

- **Drowsiness** and **confusion** are the most common side effects of benzodiazepines.
- **Ataxia** occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile.
- **Cognitive impairment** (decreased long-term recall and retention of new knowledge) can occur with the use of benzodiazepines.
- **Triazolam** often shows the rapid development of **tolerance**, early morning **insomnia**, and daytime **anxiety**, as well as **amnesia** and **confusion**.
- Drug **overdose** is seldom lethal unless other **central depressants**, such as alcohol, are taken concurrently.

BENZODIAZEPINES

BENZODIAZEPINE ANTAGONIST

- **Flumazenil** is a GABA receptor antagonist that can rapidly reverse the effects of benzodiazepines.
- The drug is available for **intravenous (IV)** administration only.
- Onset is **rapid**, but the duration is **short**, with a half-life of about **1 hour**.
- **Frequent administration** may be necessary to maintain the reversal of a long-acting benzodiazepine.
- Dizziness, nausea, vomiting, and agitation are the most common side effects.



OTHER ANXIOLYTIC AGENTS

A. Antidepressants

- **SSRIs**, such as escitalopram or paroxetine or **SNRIs** such as venlafaxine or duloxetine may be used **alone** or prescribed in **combination** with a low dose of a **benzodiazepine** during the **first weeks** of treatment.
- After **4-6 weeks**, when the antidepressant begins to produce an anxiolytic effect, the **benzodiazepine** dose can be **tapered**.
- **SSRIs and SNRIs** have a **lower potential** for physical dependence than **benzodiazepines** and have become the **first-line treatment for GAD**.



OTHER ANXIOLYTIC AGENTS

B. Buspirone

- Buspirone is useful for the **chronic treatment of GAD** and has an efficacy comparable to that of **benzodiazepines**.
- Its action is mediated by **5-HT_{1A}** and **5-HT_{2A}** receptors, although it also displays some affinity for **D₂ dopamine receptors**.
- It **lacks** the anticonvulsant and muscle-relaxant properties of benzodiazepines.
- Sedation and psychomotor and cognitive dysfunction are **minimal**, and dependence is **unlikely**.
- Buspirone does **not potentiate** the CNS depression of alcohol.



BARBITURATES

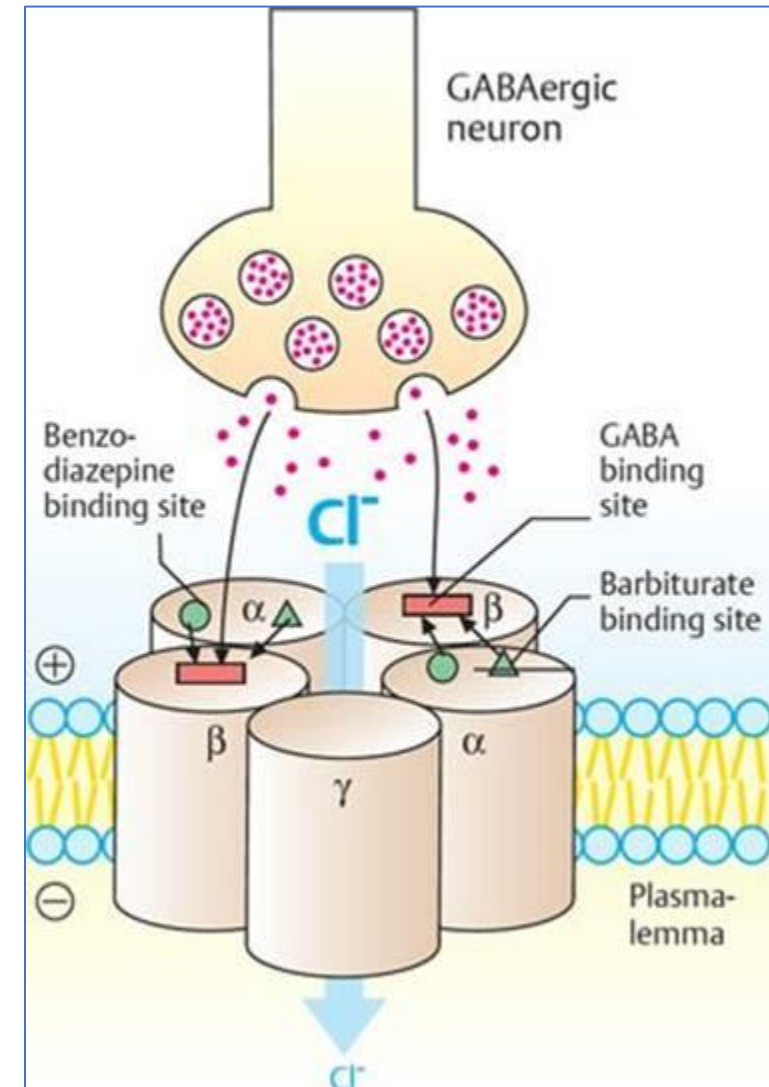
- The barbiturates were **formerly** the mainstay of treatment to **sedate patients** or to **induce and maintain sleep**.
- **Today**, they have been largely **replaced** by the benzodiazepines.
- Barbiturates induce **tolerance** and physical **dependence** and are associated with **very severe withdrawal symptoms**.
- **All** barbiturates are **controlled** substances.
- Certain barbiturates, such as the **very short-acting thiopental**, have been used to **induce anesthesia**.



BARBITURATES

A. Mechanism of action

- The **sedative-hypnotic** action of them is due to that:
 1. Barbiturates potentiate **GABA action on chloride entry** into the neuron by **prolonging the duration of the chloride channel openings**.
 2. Barbiturates also can **block excitatory glutamate receptors**.
 3. **Anesthetic concentrations of pentobarbital also block high-frequency sodium channels**.
- The **binding site** of barbiturates on the GABA receptor is distinct from that of benzodiazepines.
- All of these molecular actions lead to **decreased neuronal activity**.




BARBITURATES

B. Actions


- Barbiturates are classified according to their duration of action

Long-acting



Phenobarbital

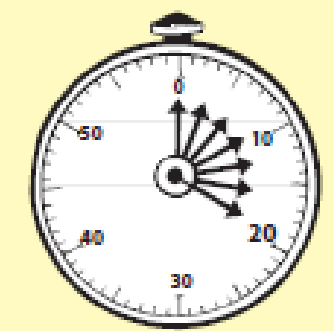
Short-acting



3-8 Hours

Pentobarbital
Secobarbital
Amobarbital

Ultra-short-acting



20 Minutes

Thiopental

BARBITURATES

B. Action

1. Depression of CNS:

- **At low doses**, the barbiturates produce **sedation**.
- **At higher doses**, the drugs cause **hypnosis**, followed by **anesthesia** (loss of feeling or sensation), and, finally, **coma** and **death**.
- Barbiturates **do not** raise the pain threshold and have **no analgesic** properties; they may **even exacerbate pain**.
- **Chronic** use leads to **tolerance**.

2. Respiratory depression:

- Barbiturates **suppress** the hypoxic and chemoreceptor response to CO₂.
- **Overdosage** is followed by respiratory depression and death.

BARBITURATES

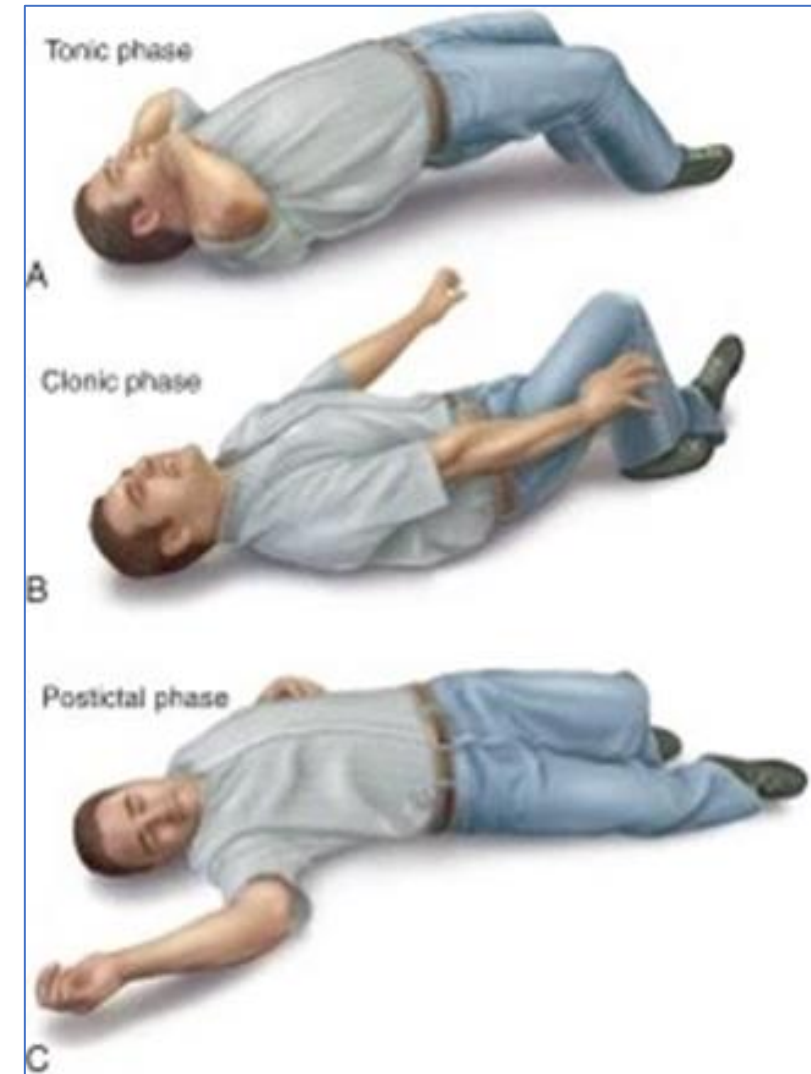
C. Therapeutic uses

1. Anesthesia:

- **Thiopental** (ultra–short-acting), has been used **IV** to induce **anesthesia**.

2. Anticonvulsant:

- **Phenobarbital** has specific **anticonvulsant** activity and it is used in the **long-term** management of **tonic-clonic seizures**.
- Similarly, **phenobarbital** may be used for the treatment of **refractory status epilepticus**.



BARBITURATES

C. Therapeutic uses

3. Sedative/hypnotic:

- Barbiturates have been used as **mild sedatives** to relieve anxiety, nervous tension, and insomnia.
- However, the use of barbiturates for **insomnia** is no longer generally accepted.
- **Butalbital** is commonly used in combination products (with acetaminophen and caffeine or aspirin and caffeine) as a **sedative** to assist in the management of tension-type or migraine headaches.



BARBITURATES

D. Pharmacokinetics

- Barbiturates are **well absorbed** after oral administration and **distribute** throughout the body.
- All barbiturates **redistribute** from the brain to the splanchnic areas, to skeletal muscle, and, finally, to adipose tissue (**short duration of action ?**)
- Barbiturates readily cross the **placenta** and can **depress** the fetus.
- These agents are **metabolized** in the liver, and **inactive metabolites** are **excreted** in urine.

BARBITURATES

E. Adverse effects

- Barbiturates cause drowsiness, impaired concentration, and mental and physical sluggishness, and occasionally, nausea and dizziness occur.
- Barbiturates **induce cytochrome P450** (CYP450) microsomal enzymes in the liver?
- Barbiturates are **contraindicated** in patients with **acute intermittent porphyria**.
- **Abrupt withdrawal** from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest.
- Barbiturates **induce cytochrome P450** (CYP450) microsomal enzymes in the liver.

OTHER HYPNOTIC AGENTS

A. Zolpidem

- Zolpidem is **not structurally** related to **BZ**, but it **selectively** binds to BZ1 receptor subtype .
- Zolpidem **has no** anticonvulsant or muscle-relaxing properties.
- It shows **few** withdrawal effects, exhibits **minimal rebound insomnia**, and **little tolerance**.
- Zolpidem has **rapidly absorbed** from the **GIT**, and it has a **rapid onset** of action and **short elimination half-life (2-3 hrs)**.
- It provides a **hypnotic effect** for approximately **5 hours**.
- Adverse effects of zolpidem include nightmares, agitation, anterograde amnesia, headache, GI upset, dizziness, and daytime drowsiness

OTHER HYPNOTIC AGENTS

B. Zaleplon

- Zaleplon is an **oral nonbenzodiazepine** hypnotic similar to zolpidem.
- However, **zaleplon causes fewer residual effects on psychomotor and cognitive function** compared to **zolpidem** or **benzodiazepines**.
- This may be due to its **rapid elimination**, with a half-life of **1 hour**.
- The drug is **metabolized** by CYP3A4.



OTHER HYPNOTIC AGENTS

C. Eszopiclone

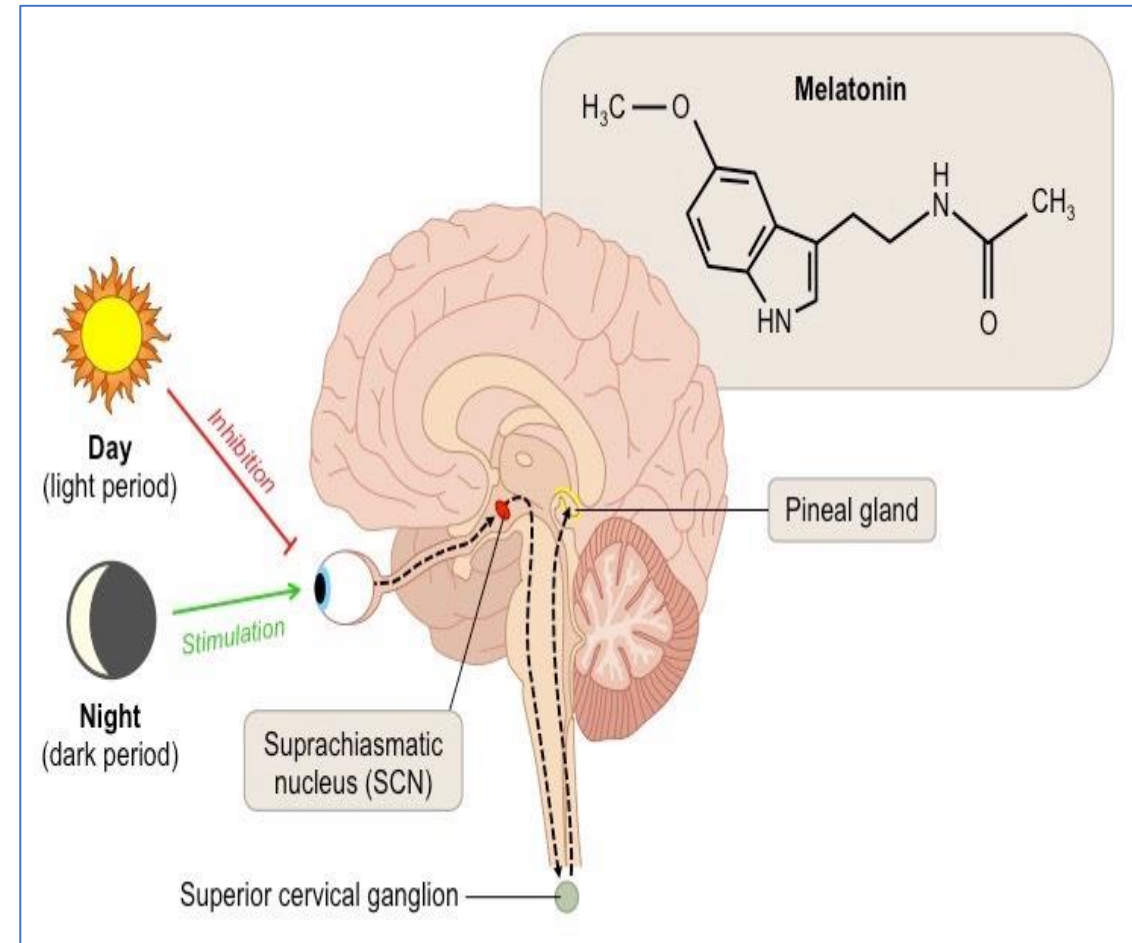
- It is an **oral nonbenzodiazepine** hypnotic, and acts on the **BZ1 receptor**.
- It has been shown to be **effective** for insomnia for up to 6 months.
- Eszopiclone is **rapidly absorbed** (peak 1 hr), extensively **metabolized** by oxidation and demethylation via the CYP450 system, and mainly **excreted** in urine.
- Elimination **half-life** is approximately **6 hours**.
- **Adverse events** with eszopiclone include anxiety, dry mouth, headache, peripheral edema, somnolence, and unpleasant taste.



OTHER HYPNOTIC AGENTS

D. Ramelteon

- Ramelteon is a **selective agonist** at the MT1 and MT2 subtypes of melatonin receptors.
- Melatonin is a **hormone** secreted by the **pineal gland** that helps to maintain the circadian rhythm underlying the normal sleep-wake cycle.
- **Stimulation** of **MT1** and **MT2** receptors by ramelteon is thought to **induce and promote sleep**.



OTHER HYPNOTIC AGENTS

D. Ramelteon

- Ramelteon is **indicated** for the treatment of **insomnia** characterized by difficulty falling asleep (increased sleep latency).
- It has **minimal potential** for abuse, and **no evidence of dependence** or **withdrawal** effects has been observed.
- Therefore, ramelteon can be administered **long-term**
- Common **adverse effects** of ramelteon include dizziness, fatigue, and somnolence.
- Ramelteon may also increase prolactin levels.

E. Antihistamines

- Some antihistamines with sedating properties, such as **diphenhydramine, hydroxyzine, and doxylamine**, are effective in treating mild types of situational **insomnia**.
- However, they have undesirable side effects (such as **anticholinergic effects**) that make them **less useful** than benzodiazepines and nonbenzodiazepines.
- Some sedative antihistamines are marketed in numerous **OTC** products.

F. Antidepressants

- The use of **sedating antidepressants** with strong **antihistamine** profiles has been ongoing for decades.
- **Doxepin**, an **older TCA agent** with **SNRI mechanisms** of antidepressant and anxiolytic action, was **recently** approved at **low doses** for the management of **insomnia**.
- Other antidepressants, such as **trazodone**, **mirtazapine**, and other older TCA with strong **antihistamine** properties are used **off-label** for the treatment of **insomnia**

**THANK YOU FOR
YOUR ATTENTION**